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Helicobacter pylori

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INTRODUCTION

At these World Congresses of Gastroenterology, papers on *Helicobacter pylori* (HP) and *Helicobacter*-related diseases will be reported by many authors. Of the more than 2000 published papers on the new spiral organism, this review can only mention the most relevant and definite new advances. The format for the review has been taken from chapters on infectious disease from the *Cecil Textbook of Medicine*. The implication of this step is that *H. pylori* is no longer a medical curiosity but has made a place for itself in the mainstream of modern medical practice. The review has been updated to include important new findings presented at Digestive Diseases Week (DDW), New Orleans 1994.

DEFINITION

Helicobacter pylori is the type species of the new genus *Helicobacter*. These organisms are curved or spiral, Gram negative, and flagellated (1), the general characteristics of most mucus-associated intestinal bacteria. *H. pylori* grows best in an atmosphere of reduced oxygen (5–15%) with added CO_2. These conditions are easily obtained in the lab by use of *Campylobacter* atmosphere generation kits, or CO_2 incubators (2). Ideal temperature is 37°C, rather than the higher temperature (42°C) required by the *Campylobacters*.

Table 1 lists important members of the *Helicobacter* genus. They have been separated from *Campylobacters* because they have sheathed flagella, a unique fatty acid profile, different respiratory quinones, and a very different 16SRNA sequence. For these reasons *H. pylori* is more related to the genus *Wollinella*, commensal of the cow rumen (3).

Notably, *Helicobacters* usually live in the stomach and require urease enzyme to colonize the mucus layer. Animal *Helicobacters* are only weak pathogens, but they do cause mild chronic gastritis and active gastritis in the wk after the initial infection. They are not definitely related to animal diseases although most colonized species are known to occasionally develop gastric erosions and/or ulcers (ferrets, cats, dogs, and pigs).

Although no ideal animal model exists for *Helicobacter pylori* and peptic ulcer, Koch's postulates have been fulfilled for *H. pylori* and gastritis in gnotobiotic pigs (4), mice (5), and monkeys (6). Important to note, *Helicobacter felis*, the organism initially cultured from cats, can colonize in the stomach of mice where it causes chronic gastritis, atrophic gastritis, and possibly even premalignant changes. This model of chronic infection mimics that present in humans in that it is not transmitted between the mice, and it is difficult to eradicate except with triple therapy regimens (see below). In addition, prevention of *H.felis* infection by oral immunization of mice with urease or *H. pylori* surface antigens implies that immunotherapy may be able to prevent or even treat human infections (7).

EPIDEMIOLOGY

Transmission

H. pylori is thought to be spread by the fecal-oral route because it can be cultured from the diarrheal stools of infected children in the Gambia (8) and occasionally from infected adults in the UK (9). *H. pylori* can easily be cultured from dental plaque in Indians (10), but only rarely can viable organisms be found in the mouth of persons in Western countries (11, 12). This indicates that oral-oral transmission (kissing or pre-mastication of food) may not be an important mode of transmission in Western countries. Evidence against oral transmission was presented at DDW by Blecker *et al* (13) who found that *H. pylori* was never transmitted to Dutch infants from their infected mothers in the first yr of life. In that study HP infection was monitored by serology and breath test.

Probably, infection between parents and children only occurs occasionally, but the presence of incontinent, ambulant young children amplifies the infectivity in a family group. In the UK, prevalence of *H. pylori* in adulthood was significantly higher if there was more than one person per room in the family home during childhood, if a bed was shared, or if there was no hot running water in the house (14). These events are really surrogate markers for large family size and lower socioeconomic status.

The source of *H. pylori* infection in some countries, for example, Peru, may be the water supply. Klein *et al* found that in order to be protected from infection,

TABLE 1
Important Members of the Helicobacter Genus

Name	Host	Features	Disease associations and other comments
H. pylori	Human	Seven sheathed flagella at one end	Causes gastritis in humans. Also sometimes found in domesticated or caged animals *e.g.*, monkeys, pigs, cats
H. mustelae	Ferret	Several randomly-placed flagella	Gastritis and erosions commonly develop in ferrets
H. helmanii (previously *gastrospirillum hominis*)	Cats, dogs, humans (rarely)	Corkscrew appearance, many flagella at one end, no axial filaments	About 1% of human gastritis cases are caused by this bacterium, presumably acquired from cats and dogs
H. felis	Cats and dogs	As for *helmanii* except also has axial filament	Isolated from a cat, can be propagated in mice, useful for a vaccine model

children in Peru needed to have a water supply from a private well with indoor plumbing (15). Socio-economic status or indoor plumbing was not protective if the children drank water from the municipal supply.

Nosocomial transmission between patients undergoing endoscopy has been reported by several authors. With manual endoscope washing, such transmission occurs in 1 to 3% of endoscopies but does not appear to occur in modern endoscopy units where endoscopes are mechanically sterilized and washed (16). The inability of gastroenterologists to adequately clean endoscopes in some countries may prevent them performing follow-up examinations after *H. pylori* therapy because patients cured of the bacterium could be re-infected. To prevent this, noninvasive testing with breath test is recommended for posttreatment assessment of patients. Where endoscopy is necessary, postprocedure administration of a single antibiotic or bismuth dose might be worthwhile.

Accidental (17) and deliberate (18, 19) infections with *H. pylori* have been reported in detail, as well as epidemics of gastritis transmitted by infected gastric secretions (20), so the acute manifestations (in adults at least) are well described (see below).

Western Countries

In general, the following statements can be made to summarize prevalence of *H. pylori* in Western countries:

a) *H. pylori* affects about 20% of persons below the age of 40 yr and 50% of those above the age of 60 yr.

b) *H. pylori* is uncommon in young children.

c) Low socio-economic status predicts *H. pylori* infection.

d) Immigration is responsible for isolated areas of high prevalence in some Western countries.

Figure 1 shows a typical prevalence curve from a developed country. The annotations describe a low prevalence in childhood, minimal increase before age 50, then a step up to a much higher prevalence after age 50. Such a curve might *incorrectly* be attributed to gradual acquisition with accelerated incidence in middle age, but such a scenario is unlikely. Most likely, the prevalence reflects decreased incidence of new *H. pylori* infections in today's children and young persons. If so, then the high prevalence in the elderly reflects long-standing infection acquired in childhood during what was (by today's standards) a lower socio-economic status for that individual. This hypothesis is supported by the fact that serological studies of sera from epidemiologists (21) and Californians (22) show that at least a 50% decline in the prevalence of *H. pylori* has occurred in the United States since 1968.

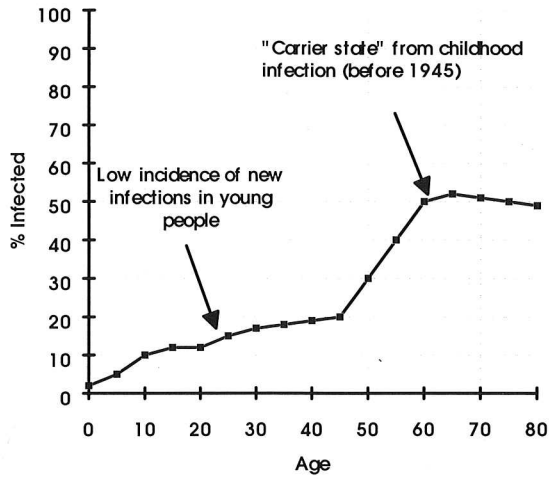

FIG. 1. Epidemiology of *H. pylori* in western countries.

Underdeveloped Countries

In most underdeveloped countries a pandemic of *H. pylori* goes unchecked, and most adults are infected. Acquisition occurs in about 10% of children per annum

between the ages of 2 and 8 yr so that most are infected by their teens. Examples of this type of epidemiology have been reported by Graham *et al* (23) and by Megraud *et al* (24). Figure 2 shows typical epidemiology for countries such as Brazil, Africa, Asia, and Eastern Europe. It is evident from these studies that the majority of persons in the world are infected with *H. pylori.*

In areas where *H. pylori* affects the majority of persons, most infections are asymptomatic, and the community tends to have other more pressing social and health care problems. In addition, even diagnosis by serology may be too expensive as are most of the available treatment options. For these reasons, only patients with severe or complicated peptic ulcer disease warrant treatment, and most physicians ignore the existence of *H. pylori.*

Virulence and Pathogenicity

H. pylori has many putative virulence factors that are listed in Table 2. Its flagella allow motility in the gastric juice and gastric mucus (25). Urease enzyme, by breaking down urea in the gastric juice, appears to generate enough bicarbonate and ammonium ion around *H. pylori* to allow its safe passage through the gastric acid barrier and its arrival at the protective mucus layer (26, 27).

The pathogenic effect of ammonia has been documented by many investigators. Ammonia elevates the pH of the gastric mucus layer from about 6 to 7 (28). It is known to deplete aerobic cells of alphaketoglutarate, an essential substrate for the TCA cycle. In rats, gastric mucosa thins if they are fed ammonia in drinking water (29). At DDW, Dial *et al* (30) reported increased gastrin RNA message in rat mucosa exposed to ammonia and agents that induce inflammation, suggesting that the hypergastrinemia present in patients with HP might be secondary to the presence of ammonia (*H. pylori* urease). Along the same lines, Khulusi

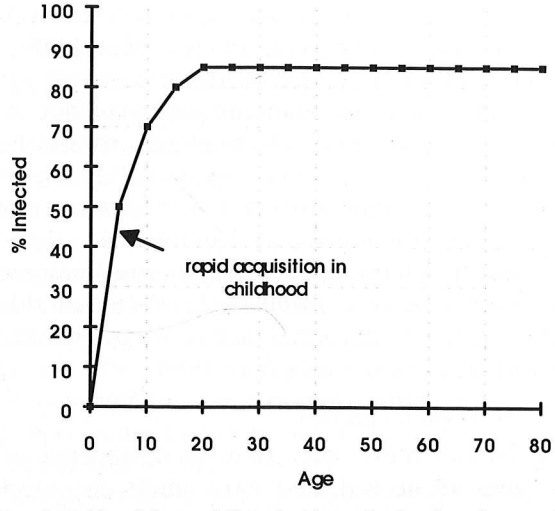

FIG. 2. Epidemiology of *H. pylori* in underdeveloped countries.

TABLE 2
Factors that Might Enhance Virulence And Pathogenicity in H. pylori

Factor	Action
Spiral shape	Allows motility in mucus
Flagella	Efficient motility in mucus
Specific attachment to phosphatidylethanolamine, GM3 ganglioside, Lewis B antigens	Selective colonization of gastric, mucus-secreting, epithelial cells
Urease	Survival in gastric environment, ammonia is toxic to epithelial cells in some animal models
Catalase	Survival in gastric mucosa and possibly within phagocytic vacuole (protection from H_2O_2)
Phospholipase	Digestion of epithelial cell membranes and mucus layer. Increased wettability of mucosa
Protease	Digestion of epithelial cell membranes and mucus layer. Increased solubility of mucus
Vacuolating cytotoxin	Damage to epithelial cells, perhaps allowing egress of nutrients from submucosa
Low molecular weight chemoattractant proteins	Attraction of neutrophils and mononuclear cells that subsequently release reactive oxygen species and interleukins

et al (31) have reported that *H. pylori* urease is increased in duodenal ulcer patients, because *H. pylori* density is greater in this group. Finally, several investigators have documented that ammonia in high concentration induces vacuoles exactly the same as those seen when cells are exposed to the vacA toxin of *H. pylori* (32). Data from Ricci *et al* (33) suggests that one role of vacA appears to be a potentiation of this effect of ammonia.

Once within the gastric mucus, *H. pylori* is able to attach to phospholipids, such as phosphatidylethanolamine (34), sialylated glycoproteins, such as ganglioside GM3 (35), and Lewis B antigens present in persons with blood group O (36, 37). Once attached to the mucus layer and mucosa, *H. pylori* delivers soluble proteases and phospholipase, which may be harmful to both the integrity of the mucus layer and the underlying cells. For example, the "wettability" of gastric mucus is increased when *H. pylori* is present (38). This may be caused by partial lysis of the phospholipid component. Although not proven to be important, impaired mucus strength may allow more luminal hydrogen ion to penetrate the mucosa.

Cytotoxin

One of the most interesting aspects of *H. pylori* pathogenicity is the so called "vacuolating cytotoxin".

This 87kDa protein is expressed in about 65% of *H. pylori* strains and is responsible for creating vacuoles in epithelial cells. These can often be seen *in vivo* in electron micrographs and can be produced *in vitro* by incubating cell cultures with *H. pylori* supernatants (39, 40). Nearly all patients with *H. pylori*-associated duodenal ulcer have an isolate that produces vacuolating cytotoxin. The gene for cytotoxin protein is called vacA and has been cloned by Cover *et al* (41). The vacA gene is present in all *H. pylori* but only produces an active protein in 65% of isolates.

A second protein at 127 kDa is called cytotoxin associated gene A, or cagA. CagA is a marker for vacuolating toxin effect, and the gene for cagA is only present when vacA cytotoxic effect is present. Antibodies to the toxin are present in nearly all duodenal ulcer patients. Theoretically, absence of cagA antibody indicates that duodenal ulcer is not present. Presence of cagA or vacA has no clinical usefulness at this time, and the exact function of cagA is unknown.

IMMUNOLOGICAL RESPONSE TO *H. pylori*

The host reaction to *H. pylori* may be an important cause of mucosal incompetence because large numbers of neutrophils and lymphocytes are attracted to the bacterium. The attraction is related to the presence of chemotactic proteins (greater than 30,000 Mwt) that are liberated by *H. pylori*. Mononuclear cells release interleukins (Il2), tumor necrosis factor, and oxygen-free radicals. Neutrophils also liberate oxygen radicals in response to the bacterium (42). The link between vacA toxin (see above) and duodenal ulceration may be a more intensive neutrophil reaction (active gastritis) with subsequent increased tissue damage (43).

The inflammatory response seems ineffective at eradicating *H. pylori*. This may be because the bacterium produces superoxide dismutase (SOD) and catalase, which protect it from being killed in neutrophil phagocytic vacuoles. SOD converts superoxide into hydrogen peroxide, and catalase then breaks down the H_2O_2 into oxygen and water, interrupting the chain of events which normally occurs.

The chronic inflammation (lymphocytes and plasma cells) seen in the lamina propria of infected patients is capable of secreting IgG and IgA. Both antibodies have been used for diagnosis by detection in serum and saliva (see below). In general, IgG is the most sensitive, but IgA falls faster after *H. pylori* eradication, so it may indicate eradication sooner than IgG (44).

Antibody production by cultured gastric mucosa has been used recently to detect an immunological history of *H. pylori* infection. If a cultured biopsy generates *H. pylori*-specific antibody bands detectable by immunoblot, then infection must be present or must have occurred at some time. This technique is able to detect immunological memory of the infection long after the bacterium has disappeared. When patients with gastric cancer were studied by this method, those without current *H. pylori* infection were usually found to have a positive immunoblot (45), *i.e.*, they had been infected with *H. pylori* in the past.

Inflammation and Carcinogenesis

The current hypothesis related to *H. pylori* and gastric cancer is that chronic inflammation selects nongastric (intestinal)-type epithelium for preferential growth in the stomach. As this mucosa replaces functioning parietal cell mucosa, acid secretion falls, and commensal bacteria intermittently colonize the stomach. These other bacteria may reduce nitrate to nitrite and then predispose to the formation of carcinogenic nitrosamines (46).

A second mechanism proposes that the chronic inflammatory cells generate superoxide and nitric oxide, which can form both reactive oxygen species and nitrosamine (47) with subsequent carcinogenic effects (48).

Supposedly, chronic gastritis leads to intestinal metaplasia (atrophic gastritis), which then undergoes malignant change. Recent data presented in abstract form suggests that eradication of *H. pylori* halts this process and removes a key factor in the chain of events (49).

The carcinogenic effect of *H. pylori* infection is modulated by dietary and perhaps other environmental factors. Sobala *et al* (50) have documented falls in gastric vitamin C levels in *H. pylori* infected patients. Vitamin C is an antioxidant and prevents the formation of nitrosamines in the stomach.

There is also epidemiological evidence to support the role of other factors in the causation of gastric adenocarcinoma. In the United States, most people were infected with *H. pylori* until about 1960, but gastric cancer rates fell precipitously starting around 1930 (51). This may have been related more to improved diet and standard of living than falling *H. pylori* status.

At DDW, Blaser *et al* (52) shed more light on this subject. They detected a significantly higher incidence of gastric cancer in Japanese Hawaiians of high birth order than of low birth order. The hypothesis is that the last born child, because of association with many *H. pylori* infected siblings, would acquire *H. pylori* at a much younger age than a first born child. Thus, the increased risk of gastric cancer in last born children could be caused by younger acquisition of the infection. If so, then a small decline in the incidence of *H. pylori* could have sudden and dramatic effects on gastric cancer risk.

CLINICAL MANIFESTATIONS

Duodenal and Gastric Ulcer

The most obvious disease associated with *H. pylori* is peptic ulceration. Figure 3 summarizes the associa-

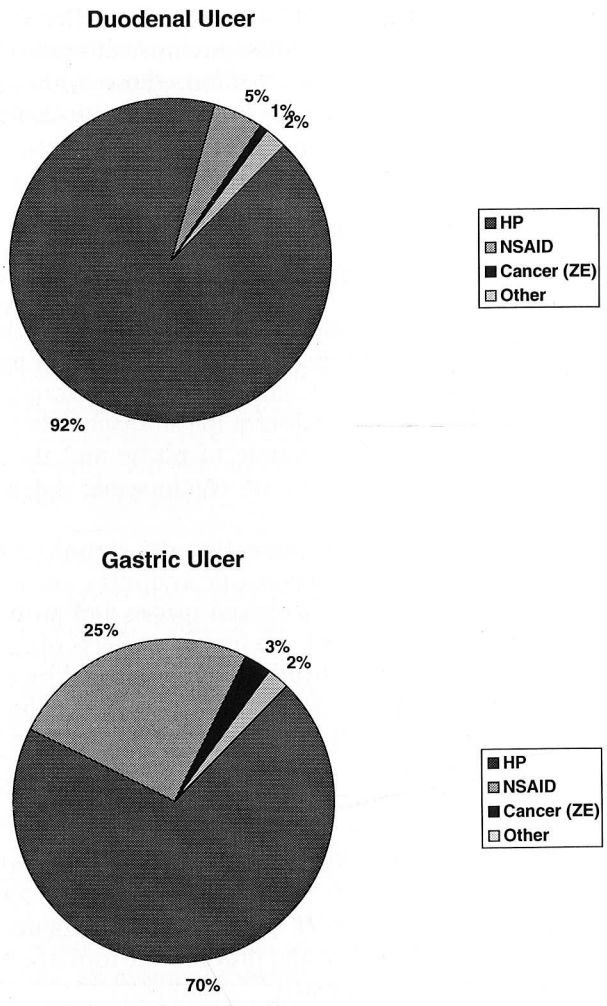

FIG. 3. Association between *H. pylori* and peptic ulceration.

tion. Essentially, more than 90% of duodenal ulcers (DU) are caused by *H. pylori*. When a patient with DU does not have *H. pylori*, etiological factors such as Zollinger-Ellisson syndrome or nonsteroidal inflammatory drug (NSAID) use are likely (53).

In gastric ulcer, two causes prevail, and many patients will exhibit both. Most gastric ulcers have *H. pylori*, and these can be identified by presence of the bacterium and/or chronic gastritis. The stomach is also directly exposed to ingested agents such as NSAID and is more likely than the duodenum to ulcerate in response to these agents. Therefore, in the United States, about 35% of gastric ulcers are not associated with histological chronic gastritis or *H. pylori* but are caused by NSAID.

Other etiologies can also be suspected or proven by the histological appearance of the mucosa, Zollinger-Ellisson syndrome and gastric cancer being two less common causes of gastric ulcer other than *H. pylori* and NSAID.

Association With Malignancy

There are two cancers associated with *H. pylori*. Gastric carcinoma and lymphoma of the 'mucosa associated lymphoid tissue' (MALT).

Adenocarcinoma. The incidence of this lesion has declined in the United States since 1930. At that time it was the most common cancer, but now it ranks about ninth. The current incidence is only 6 per 100,000 persons per annum, a decline from 50 in 1930 (22). Worldwide, however, gastric cancer is the second most common cancer, examples of high prevalence areas being Brazil, Colombia, Korea, China, and Japan. *H. pylori* infection affects more than half the population in all these countries (54).

There are two histological types of gastric cancer, so called diffuse (anaplastic - 'cignet ring') and intestinal (well differentiated adenocarcinoma). It is the latter (epidemic) type that is most increased in prevalence in Third World countries and is strongly associated with *H. pylori* (both types are increased in HP-infected persons). The decline of gastric cancer in the United States might be partially explained by a falling incidence of *H. pylori* infection since 1930 and a decrease in incidence of the intestinal type of gastric cancer.

In an extensive review of gastric cancer and *H. pylori* (54), the Eurogast Study Group determined that presence of *H. pylori* confers an approximately 6-fold risk of gastric cancer, accounting for about half of all gastric cancers. Related work by investigators in Leeds, UK (17), including observations during an acute *H. pylori* infection, suggests that the factors important to carcinogenesis are hypo- or achlorhydria followed by a decline in ascorbic acid levels in the gastric juice. Vitamin C, an antioxidant, normally prevents formation of nitrosamine carcinogens that might otherwise result from the inflammation and bacterial colonization.

Lymphoma. Mucosa-associated lymphoid tissue (MALT) may undergo malignant change, causing a low-grade lymphoma of the stomach. Retrospective biopsy studies show that 90% of such MALT lymphomas are associated with *H. pylori* (55). Histologically, many lymphoid follicles are seen in the mucosa that, if stained for immunoglobulin, are shown to be monoclonal. In normal *H. pylori*- associated gastritis, lymphoid follicles are also seen, but they mostly regress after effective therapy of *H. pylori*.

In the initial report of the association, Wotherspoon *et al.* (56) found that 92% of 110 MALT lymphomas were associated with *H. pylori* compared with 50% of control cases. Subsequent reports suggest that these tumors are sometimes driven by continuing *H. pylori* antigenic stimulus and regress when *H. pylori* is treated (57, 58). In a recent abstract the German MALT-Lymphoma Study Group (59) reported that apparent cure of MALT lymphoma occurred in half the patients in whom *H. pylori* was eradicated. In the future, *H. pylori* therapy may be the initial step in the treatment of proven or suspected gastric lymphoma.

DIAGNOSIS OF *H. pylori*

The use of various available diagnostic tests is outlined in Table 3. The actual test chosen would depend on the enthusiasm of the physician, the type of patient, and the type of practice. Various scenarios are given below.

Patients who Require Endoscopy

Histology and rapid urease test. At endoscopy, the simplest method of diagnosis is mucosal biopsy, either for histology or for rapid urease test (*e.g.*, CLOtest). If *H. pylori* diagnosis is going to make an important contribution to management then the most sensitive test should be used. Currently this is histology. The cost of histology must be taken into account, however, and in most cases the urease test offers an inexpensive alternative.

Our practice is to do both tests and to discard the histology specimen if the CLOtest turns red on the day of the endoscopy. In patients with a negative CLOtest, the mucosa is usually normal (90%) but 5–10% will have low numbers of *H. pylori* not detected by the CLOtest (60). The presence or absence of *H. pylori* will help determine the etiology of ulcer disease because Zollinger-Ellisson syndrome and NSAID-induced lesions are not associated with chronic gastritis (53).

Culture. Culture of *H. pylori* should be used if antibiotic sensitivity of the organism is required. This is especially important in patients who have antibiotic allergies, or who have failed previous therapies, or in countries where *H. pylori* has a high level of background antibiotic resistance. Biopsies for culture should be kept moist in a single drop of saline and plated within 2 h of endoscopy. *H. pylori* grows in 3–6 days on chocolate or brain-heart infusion blood agar, in a 10% CO_2 incubator or Campy pac atmosphere at 37°C. Most labs can culture the organism easily. Identification is by presence of Gram-negative curved bacteria, rapid urease+, catalase+, and oxidase+.

If culture cannot be performed close to the endoscopy room, snap freezing biopsies on dry ice in skim milk with 17% glycerol mixture allows shipping to the mi-

TABLE 3
Diagnosis of Helicobacter pylori

Method	Specimen	Sensitivity	Specificity	Comment on usage
Quick serology test in office (subject to CLIA88 regulations)	Serum (separated from clotted blood)	95%	85%	Performed in 10 minutes on serum. Gives yes or no answer. Use to exclude/confirm *H. pylori* (*e.g.*, ulcers) in appropriate setting.
*Quick saliva test in office	Saliva/gingiva (detects IgG)	90%	85%	Performed in 10 minutes on oral swab/saliva. Gives yes or no answer
Machine read ELISA done in lab	Serum	95%	95%	Provides titer (OD) so that fall in antibody titer can be assessed. Patients with rapid antibody fall are cured. Persistent antibody after therapy is common and may slowly fall (12–18 mo), representing cure, or may indicate continued infection.
*Urea breath test (at some centers)	Breath sample	95–98%	95–98%	Urease of *H. pylori*, active in the gastric mucus layer of the stomach, generates labeled CO_2 from breakdown of ingested urea. Breath sample taken 20–40 minutes after fasting patient ingests isotope in liquid (c^{13}) or capsule (c^{14}). Sample is mailed to lab. C^{13} test has no radiation but costs more. C^{14} test is less expensive and simpler.
Urease test of biopsy	One mucosal biopsy	90–95%	98%	Simple biopsy test done at endoscopy. Urease of *H. pylori* generates ammonia and causes pH change. One-step test, no reagents, result in 20 minutes.
Histology, Giemsa stain ×2	Two mucosal biopsies	98%	98%	Available to all gastroenterologists. Simple and very accurate. Specimen can be re-examined in equivocal cases. Provides a permanent record.
Culture of biopsy	One mucosal biopsy	90–95%	100%	Antibiotic sensitivity information may help guide therapy in refractory patients. Commonly used in research setting.
Culture of stool	Stool sample	30–50%	100%	Antibiotic sensitivity information is possible. Only used in research setting at present.
Polymerase chain reaction	Stool sample, gastric juice, or biopsy of stomach	95%	95%	Experimental at present. False positive reactions limit use as gold standard method.

* Not approved by the FDA.

crobiology lab with minimal loss of viability during the first month (61).

Note that elective endoscopy might be postponed for 1–2 wk if the patient has taken medication that would interfere with *H. pylori* diagnosis *e.g.*, Pepto Bismol (bismuth), antibacterial agents, or omeprazole (62).

Noninvasive Diagnosis

Serology. Serology is the simplest and most widely available diagnostic test. Usually IgG is elevated in persons with *H. pylori.* Because *H. pylori* is a chronic infection that does not resolve spontaneously, elevated IgG indicates active infection, unless the patient is known to have been treated for *H. pylori* in the recent past (2 yr).

Two types of serological tests are currently available. The rapid office tests are sensitive, but at present give 10% false positive results, so they may need to be confirmed with a laboratory-based test in some patients (see below). Nevertheless, in the office setting, sensitive tests are able to exclude the diagnosis of *H. pylori*, so they can direct work-up away from peptic ulcer disease and gastritis, perhaps toward pancreatic or biliary disease. If rapid tests are less specific, they can be supplemented by another confirmatory method such as laboratory-based enzyme-linked immunosorbent assay (ELISA) (see below) or breath test.

The laboratory-based serology tests are able to quantitate the actual amount of antibody present. These tests should be used to obtain a baseline antibody titer when treatment of *H. pylori* is planned. This then allows serological follow-up after therapy. For example, titers obtained 1, 3, and 6 months posttherapy usually show a consistent fall in successfully treated patients (44).

Although not generally available, rapid tests using salivary and/or gingival IgG and IgA secretion have been evaluated for detection of *H. pylori.* Although less accurate than the best serum ELISA methods, these tests may be equal to rapid office tests, are simpler, and may be particularly appropriate for children. In one evaluation study reported by Megraud *et al* (63), the results for the gingival transudate were the following: sensitivity 89% (17/19), specificity 98% (59/60), PPV 94% (17/18), and NPV 96% (59/61).

Breath Tests

Breath tests measure the actual presence of *H. pylori* in the stomach by detecting its urease enzyme. Breath tests are highly specific (98%) and very sensitive (95%). They can indicate cure of *H. pylori* 4 wk after antibiotic therapy, at a time when antibody tests will still give a positive result. Breath tests can give false positive results in patients who have had gastric surgery or who take omeprazole (achlorhydria). False negative breath tests easily occur in the same situations, but especially in patients who secretly take Pepto Bismol or antibiotic in the days before the test.

For the ^{13}C-urea test patients eat a 120 ml high calorie meal (to delay gastric emptying of the isotope) then drink ^{13}C-urea solution 10 minutes later. Breath is transferred from a collection bag to vacutainers. Samples are taken at intervals for about 1 h and mailed to the lab. Various modifications exist. The European "standard"^{13}C-urea breath test uses a simplified method with only one or two samples taken (baseline and 30 minutes) (64).

The ^{14}C-urea test is very similar but may be performed without giving a meal and can be read immediately in a scintillation counter (available at most universities). The ^{14}C-urea test exposes the patient to radiation equivalent to one thousandth of an upper GI series and is simpler than the ^{13}C test.

Breath tests are investigational at present (July 1993) but are being used in clinical trials in the United States at several centers.

Therapy

General Principles

Therapy should not be given unless a diagnostic test for *H. pylori* has been performed and a positive result obtained. Even duodenal ulcers are not universally infected with *H. pylori.* In fact, the absence of *H. pylori* in peptic ulcer is a diagnostic pointer to an unusual and perhaps more serious etiology (65).

There is no justification for treating patients longer than 14 days. Cure rates have been less with shorter therapies but longer therapies have not been shown to result in higher cure rates. If 14-day therapy fails, the bacterium is probably resistant to that antibiotic combination and future therapy may need to be guided by antimicrobial sensitivity testing of a cultured organism.

Compliance decreases with longer or more complicated therapy. If compliant patients develop severe side effects, they may terminate therapy at 7 days by which time most infections have been eradicated.

If therapy fails, do not use the same combination again. *H. pylori* easily becomes resistant to metronidazole and clarithromycin so these agents should not be used twice unless antibiotic sensitivity data is available to support their continued use. Even when antibiotic resistance does not develop (for example, with amoxicillin therapy), experience has shown that patients do better on a different antibiotic therapy than with a second course of the same therapy. After therapy, avoid antimicrobial agents and omeprazole for at least 4 wk before doing a diagnostic test (biopsy for histology and urease test or breath test) to confirm eradication (Fig. 4). The potential interfering effect of omeprazole on diagnosis of *H. pylori* has been noted by several inves-

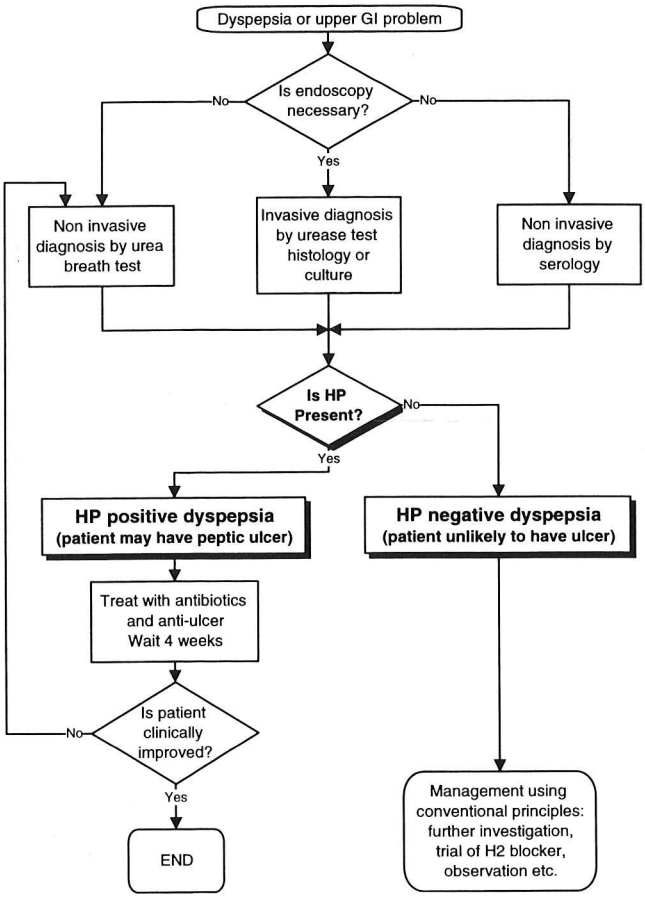

FIG. 4. Algorithm for management of peptic ulceration (and dyspepsia).

tigators at DDW (1994) (66, 67). While on omeprazole, *H. pylori* density decreased in the antrum and increased in corpus mucosa.

To prove cure with serology, serological studies should demonstrate a falling antibody titer at several points over 6 months or a decline to less than 50% of the initial pretreatment value.

DEFINITION OF CURE

Cure is defined as failure to demonstrate *H. pylori* by a sensitive technique 4 wk after the patient has ceased all antimicrobial therapy and proton pump inhibitors. The most reliable and reproducible technique is still gastric biopsy for histology (95–98% with two samples) although culture is almost as sensitive in expert hands (95%+).

The urea breath test is also a valid method (95%+) provided that the patient has not had previous gastric surgery.

Reinfection

Reinfection is uncommon in Western countries, usually less than 1% per annum. Data to support this comes from a study by Forbes *et al* (68) in which patients in Perth, Australia were followed up 7 yr after *H. pylori* eradication. Reinfection rate was less than 1% per annum, similar to that reported earlier by Borody (69). Because spouses are often infected with *H. pylori*, one might ask whether or not infected spouses need to be treated to prevent re-infection of the patient. Cutler *et al* (70) noted that the presence of an infected spouse does not affect cure rate. Thus early reinfection (before 1 month) seems to be rare.

Reinfection in children may be more common according to data reported by Oderda *et al* (71). In that report, reinfection rate was 18% after 1 yr. Thus eradicative therapy may not provide a permanent cure in children where infected siblings provide an easy source of reinfection (72). It might be useful therefore to screen for and treat all *H. pylori* in the family when the index case is a child.

Antibacterials That Can be Re-used

Antimicrobial drugs that do not induce resistance in *H. pylori* are described in Table 4. The most useful of these are amoxicillin, tetracycline, and bismuth. One or two of these agents are usually given in combination with metronidazole, clarithromycin, or omeprazole.

Antibacterials That Lead to Resistance

Antimicrobials that are known to induce resistance are listed in Table 5. In general, resistance develops because all populations of *H. pylori* have resistant organisms present in very low numbers (10–10) that are selected out when single antimicrobial therapy is used. The use of a second drug concurrently to suppress *H. pylori* greatly reduces the chance of selecting out the resistant clone. For example, cure rate with metronidazole alone is virtually nil, but therapies of metronidazole with bismuth, or metronidazole with amoxicillin, cure greater than 80% of sensitive *H. pylori* strains.

Bismuth-based Therapies

Bismuth-tetracycline-metronidazole "triple therapy". As mentioned above, dual therapies with bismuth and metronidazole have high cure rates for susceptible isolates, but it is not cost effective to routinely obtain antibiotic sensitivity results before therapy. Therefore, the 'triple therapy' regimens are preferred because these eradicate approximately 50% of metronidazole-resistant isolates, giving ultimate cure rates of 85–90%.

The disadvantages of triple therapy (bismuth, tetracycline, metronidazole) are the number of tablets (at least 15 per day currently), the duration of therapy (10–14 days), and side effects, such as diarrhea in 25–35% of patients. None of the side effects are disabling or long-lived, and patients may prefer triple therapy because of its low cost ($42 US).

The minimal duration of triple therapy is thought to be 12 days, the optimal dose frequency is 5 times per

TABLE 4
Antibiotics that can be Re-used and Do Not Induce Antibiotic Resistance in H. pylori

Drug	Dose	Duration	Comment
Amoxicillin	500 mg *q.i.d.* or 1 G *b.i.d.*	7–14 days	Occasional *C. difficile*
Tetracycline	500 mg *q.i.d.*	7–14 days	In triple therapy
Furazolidone	100 mg *q.i.d.*	14 days	Variable efficacy as single agent (20–50%)
Bismuth subcitrate (CBS, De-Nol)	110 mg (1 tab) *q.i.d.*	14 days	Variable efficacy as single agent (20–40%), use in triple or dual therapy
Bismuth subsalicylate (BSS, Pepto-Bismol)	512 mg (2 tabs) *q.i.d.*	14 days	As for CBS

TABLE 5
Antibiotics that Do Induce Antibiotic Resistance in H. pylori (therefore should not be routinely re-prescribed in the same patient)

Drug	Dose	Duration	Comment
Metronidazole (and other nitroimidazoles)	750 mg-1000 mg/day	7–14 days depending on combination	May interact with alcohol, reversible neuropathy and CNS side effects with long duration high doses, but usage should be limited to 14 days, 1 G daily in HP therapy
Clarithromycin (and other macrolides)	500–1500 mg per day	7–14 days	Unpleasant taste, disturbance limits dose to 1000 mg/day in most persons

central nervous system.

day, and almost 100% eradication can be achieved if it is combined with omeprazole (73).

Bismuth has a short half-life in the gastric mucus layer, so frequent dosing (at least *q.i.d.*) is preferred. Because most *H. pylori* infections are cured in the first wk, patients with severe side effects may discontinue the drug after that time.

Omeprazole-based Therapies

Amoxicillin 1 G b.i.d., omeprazole 20 mg b.i.d. This therapy has been compared with triple therapy by Labenz *et al* (74). In their study the two therapies were comparable for efficacy, but side effects were far less in the amoxicillin-omeprazole combination. The cost of this therapy is $130 US (75). After further evaluation in 1993–4, the consensus is that this therapy has a cure rate of 80% on average (almost equal to triple therapy). In order to enhanced the cure rate, 4 times daily dosing (500 mg *q.i.d.*) of amoxicillin and even supplementation with 1 G daily of metronidazole is recommended by Lammouliatte *et al* (76).

Clarithromycin 500 mg b.i.d., omeprazole 20 mg b.i.d.. Logan *et al* (77) has achieved an 80% cure rate with this therapy. Side effects are very low. Treatment failures may leave macrolide-resistant *H. pylori*. This may be the best treatment for penicillin allergic patients who have failed triple therapy and are assumed to have a metronidazole-resistant isolate.

Other Therapies

Hentschel: amoxicillin-tinidazole-ranitidine. In a large, double-blind study described by Hentschel *et al* (78), cure rate approximated 90% with a 14-day course of amoxicillin (500 mg *q.i.d.*), metronidazole (250 mg *q.i.d.*), and ranitidine (150 mg *b.i.d*).

Refractory Patients

Omeprazole-clarithromycin-amoxicillin. This combination gives a cure rate of 90% (76). The duration of therapy has not been optimized, and a shorter therapy may be possible.

Omeprazole, with amoxicillin or clarithromycin, plus metronidazole. These combinations give cure rates of around 90% (76). Duration of therapy may be shortened to 1 wk with some omeprazole-macrolide-metronidazole regimens. A low-dose rapid cure therapy using clarithromycin 250 mg *b.i.d.*, tinidazole 1 G daily, and omeprazole 20 mg daily described by Bazzoli *et al* (79) costs $90 US and gives high cure rates in 7 days. I prefer to use slightly higher doses of clarithromycin (500 mg *b.i.d*) and at least 20 mg *b.i.d.* of omeprazole in this regimen.

Intravenous amoxicillin 1 G t.i.d. and oral omeprazole 14 days. In noncompliant patients, 14 days of this therapy has resulted in cure rates approaching 80%. This suggests that high systemic levels of amoxicillin can penetrate the gastric mucosa to kill *H. pylori* (80).

RECOMMENDATIONS FOR THERAPY

At this time there is some dispute about the most effective and proven therapies. My own preferences are shown in Table 6. The doses and durations shown may err slightly on the high side of what has been published, but, until comparative studies are performed in the United States, I think it is better to err on the side of

TABLE 6
*Current Best Choices for H. pylori Therapy**

Rx1: Take the following for 2 wk (cure rate 80%+): [USA] PB tablets, 2 tabs 4 times daily (with meals and at bedtime); tetracycline, 500 mg 4 times daily (same times as PB); metronidazole, 250 mg 4 times daily (same times as PB). [Europe, UK and Australia] DeNol tablets, 1 tabs 4 times daily (with meals and at bedtime); tetracycline, 500 mg 4 times daily; metronidazole, 250 mg 4 times daily.

Rx2: Take the following for 2 wk (cure rate 80%+): Amoxicillin, 500 mg 4 times daily; metronidazole, 250 mg 4 times daily; omeprazole, 20 mg twice daily.

Rx3: Take the following for 1 wk (cure rate 90%): Clarithromycin, 500 mg twice daily; metronidazole, 250 mg 4 times daily; omeprazole, 20 mg twice daily.

Rx4: Take the following for 2 wk (cure rate 90%+): Amoxicillin, 500 mg 4 times daily; clarithromycin, 500 mg twice daily; omeprazole, 20 mg twice daily.

Rx5: Take the following for 2 wk (cure rate 70%+): Amoxicillin, 500 mg 4 times daily; metronidazole, 250 mg 4 times daily; Ranitidine, 150 mg twice daily.

Rx6: Take the following for 14 days (cure rate 80%+): Amoxicillin, 500 mg 4 times daily; clarithromycin, 500 mg 3 times daily, (omeprazole not necessary).

Rx7: Take the following for 14 days (cure rate 80%+): Omeprazole, 20 mg twice daily; clarithromycin, 500 mg 3 times daily (omeprazole not necessary).

* Notes taken from DDW (1994) abstracts: Many investigators have been unable to achieve high cure rates with just omeprazole and amoxicillin. Therefore I recommend addition of metronidazole, as in Rx2.

If patient has had metronidazole therapy before (and failed therapy), *Helicobacter pylori* has usually developed resistance. Therefore omit this drug from the Rx2 and Rx3 regimens or use Rx4 or Rx6/Rx7.

Best cure rate in comparative studies has been with Rx4 (76). Rx1 gives a greater than 90% cure with lower dose and 5 times daily dosing if patient is well motivated and very compliant. Add omeprazole to Rx1 to give close to 100% cure rate (73).

PB, Pepto Bismol.

overtreatment rather than have to deal with antibiotic resistant relapsing *H. pylori*.

Inexpensive Therapy Possible in Latin America

Gutierrez *et al* (81) have been able to eradicate 72% of *H. pylori* with a 4-wk course of furazolidone 100 mg *q.i.d.*, and bismuth subsalicylate 2 tabs *q.i.d.* This may prove to be the least expensive therapy available in areas where metronidazole resistance is high. Furazolidone does not induce resistance in *H. pylori*, so it has an advantage over combinations using nitroimidazoles or macrolides.

PROGNOSIS

Asymptomatic Gastritis

In Western Countries, several follow-up studies have shown an incidence of 1% per annum in development of peptic ulcer disease for persons with *H. pylori* gastritis. Thus, lifetime ulcer rates for these persons are 30–50% (82). According to the study of Parsonnet *et al* (22), lifetime risk of stomach cancer in asymptomatic infected persons is about 0.5% in the United States but could be more in underdeveloped countries. Currently, screening and therapy of asymptomatic gastritis in Western countries is only marginally cost-effective (about $20,000 per yr of lives saved in the USA) and is not advocated. In subgroups with higher gastric cancer risk, for example patients with a family history of gastric cancer, *H. pylori* eradication is appropriate.

Nonulcer Dyspepsia

Several studies have addressed the issue of nonulcer dyspepsia (NUD) and *H. pylori*. The most notable of these recently published was that of O'Morain *et al* (83). In that study, because of a strong placebo response, initial observation could not demonstrate any major benefit of *H. pylori* eradication in NUD patients. After 1 yr, however, improvement had been maintained in the HP negative patients whereas patients with persistent HP had mostly relapsed. Further studies are under way to evaluate this dilemma using long follow-up (1 yr) after double-blind eradicative therapy.

Duodenal Ulcer

All double-blind studies reported to date have shown improved ulcer healing and decreased relapse rate for duodenal ulcer in which *H. pylori* has been eradicated. According to NIH guidelines (NIH consensus conference, Washington DC, February 1994), management of duodenal ulcer must include assessment of *H. pylori* status and eradication of the organism. Overall, permanent duodenal ulcer cure rates of 90% are seen. About 10% of patients still have ulcer relapse, usually due to persistent basal acid hypersecretion or some other undetermined permanent mucosal defect (84).

An important advance over the past 5 yr has been the discovery that somatostatin deficiency occurs in gastric antrum infected with *H. pylori*. Initially, hypergastrinemia was noted, but acid output was not obviously increased in the patients (85). Subsequently it was discovered that immunoreactive somatostatin, D cells, and somatostatin message were all decreased in patients with gastritis. This abnormality was related more to the inflammation than the actual presence of *H. pylori*. According to El Omar *et al* (86), basal acid secretion is increased 6-fold in duodenal ulcer patients but falls back toward normal in the 6 months after *H. pylori* eradication. These factors provide a plausible link among *H. pylori*, gastritis, acid hypersecretion, and peptic ulceration.

Gastric Ulcer

In gastric ulcer, two causes prevail, and many patients will exhibit both. Most gastric ulcers have *H. pylori*,

and these can be identified by the presence of the bacterium and/or chronic gastritis. The stomach is also directly exposed to ingested agents such as NSAID and is more likely than the duodenum to ulcerate in response to these agents. Therefore, in the United States, about 35% of gastric ulcers are not associated with histological chronic gastritis or *H. pylori* but are caused by NSAID.

Other etiologies can also be suspected or proven by the histological appearance of the mucosa; Zollinger-Ellisson syndrome and gastric cancer are two less common causes of gastric ulcer other than *H. pylori* and NSAID.

PREVENTION

Immunization

Antimicrobial therapy and immunization will both be needed in the campaign against *H. pylori*. In western countries, antibiotic therapy of *H. pylori* might eliminate the disease because new infections are rare, even in children. In underdeveloped countries, however, there may be a role for vaccination because water supplies may be contaminated, and reinfection will soon occur in treated patients (94).

The most successful animal model for vaccine study has been the mouse infected with *H. felis*. These mice develop a chronic infection that is not transmitted to other mice and that cannot be easily eradicated (5). By giving *H. pylori* antigens orally (usually urease) in combination with hydroxyapatite and cholera toxin, mice can be protected from *H. felis* infection. Even more exciting is the report from Corthesy-Theulaz *et al* (95) in which mice were actually able to eradicate the *H.felis* infection after being immunized with the above antigen/adjuvent combination.

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